

Evaluation of cardiovascular risk factors, prevalence and determinants of coronary artery disease in renal transplant patients: a single center experience

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ABSTRACT

Aims: Cardiovascular disease is the leading cause of morbidity and mortality in renal transplant patients. In our study, we aimed to determine the cardiovascular (CV) risk factors, the prevalence and determinants of coronary artery disease (CAD) in patients who underwent kidney transplantation in our center.

Methods: One hundred sixty nine patients who underwent kidney transplantation in our center were included in the study retrospectively. Demographic and clinical characteristics of the patients, cardiac evaluation findings and further examination results were scanned from the database of our center.

Results: The mean age of the patients was 42.86 ± 12.97 years and 43.19% were female. The most common etiological factors for the development of end-stage renal disease were hypertension (HT) and diabetes mellitus (DM). Ninety seven patients (57.4%) were undergoing dialysis, 4 of whom were on peritoneal dialysis. Renal transplant was performed from a cadaver in two patients and from a living donor in the other patients. CAD was detected in 29 patients (17.15%). The most prevalent CV risk factors were HT and hyperlipidemia (HL). Multivariate logistic regression analysis revealed that age, DM, HL and dialysis history were independent risk factors for the development of CAD. In the postoperative follow-ups, no death or acute coronary syndrome was observed during the hospitalization period.

Conclusion: Prevalence of CV risk factors is high in renal transplant candidates. Our findings support the need for a detailed cardiac evaluation and effective management of CV risk factors in patients preparing for kidney transplantation.

Keywords: Renal transplantation, end-stage renal disease, preoperative cardiac evaluation, cardiovascular risk in renal transplant patients

INTRODUCTION

Kidney transplantation is the most beneficial treatment modality that improves the quality of life and survival of the patients with end-stage renal disease (ESRD).¹ Thousands of patients all over the world are on the kidney transplant waiting list.² There are approximately 70,000 ESRD patients in Turkey and approximately 3000 kidney transplants are performed annually, 77% of which are from living donors.³

Cardiovascular diseases (CVD) are found in approximately half of the patients with advanced kidney disease and are responsible for 40-50% of all deaths in these patients.^{4,5} These rates are higher in dialysis patients.⁶ In addition to common risk factors such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), volume overload and hormonal changes in patients with chronic kidney disease (CKD) also affect cardiac structure and

functions and increase cardiac events in these patients.^{7,8} Although CV risk decreases after renal replacement, CV complications are responsible for a substantial portion of perioperative morbidity and mortality.^{9,10} Therefore, cardiac examination before kidney transplantation becomes more important.

There is no consensus on cardiac evaluation previous to kidney transplantation, between the cardiology and nephrology societies, and European and American guidelines. In the 2022 European Society of Cardiology (ESC) guidelines for CV assessment of non-cardiac surgery, there is no assessment recommendation for patients undergoing kidney transplantation, which is considered a moderate risk surgery. Biomarkers, ECG, and functional capacity assessment are only recommended for patients aged 65 and over who will undergo moderate

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and high risk surgery.¹¹ The 2020 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline recommends that all transplant candidates be evaluated for CVD, ECG should be taken for all patients, symptomatic patients should be referred to cardiology, and patients with high risk of coronary artery disease (CAD) or low exercise capacity should be screened for CAD with non-invasive tests.¹²

The aim of our study was to determine the demographic characteristics, cardiovascular risk factors, prevalence and predictors of coronary artery disease in kidney recipients in our center.

METHODS

The study was carried out with the permission of Koç University Ethics Committee (Date: 26.08.2019, Decision No: 2019.265.IRB2.087). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This is a retrospective study including 169 patients with ESRD who underwent cardiology evaluation before kidney transplantation in our center between 2018 and 2020. Demographic and clinical characteristics of the patients, cardiac evaluation findings and further examination results were scanned from the database of our center. Hypertension was defined as repeated office systolic blood pressure (SBP) values ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg.¹³ Diabetes mellitus was defined as a fasting plasma glucose levels of ≥ 126 mg/dl or a 2-hour post-load glucose levels of ≥ 200 mg/dl.¹⁴ Hyperlipidemia was considered as total cholesterol level ≥ 200 mg/dl or low density lipoprotein (LDL) levels of ≥ 130 mg/dl or triglyceride levels of ≥ 150 mg/dl.¹⁵

The blood samples of the patients were taken in the morning fasting, and in the patients undergoing dialysis, they were taken before dialysis. Estimated glomerular filtration rate (eGFR) were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for adults.¹⁶ End stage renal disease (ESRD) was defines as eGFR < 15 mL/min.¹⁷

Cardiac Evaluation

Cardiac examination and non-invasive tests were performed on the same day and on non-dialysis days. The Epiq 7C ultrasound system (Philips, Andover, MA, USA) equipped with a 2.3-3.5 MHz transducer probe was used for transthoracic echocardiographic (TTE) evaluation. All measurements were made in line with the current recommendation guidelines of the American Society of Echocardiography.¹⁸

Treadmill exercise test was performed on eligible patients. Patients who were unable to perform the test or who were

considered to have non-diagnostic test were referred to other non-invasive tests like myocardial perfusion scintigraphy (MPS) or coronary computed tomography (CT) angiography by the evaluating cardiologist. Conventional coronary angiography (CAG) was performed in patients who were found to have ischemia or findings supporting significant CAD in non-invasive tests. A stenosis of 50% or more in the coronary arteries was accepted as obstructive CAD. Revascularization with percutaneous coronary intervention (PCI) or coronary artery by-pass graft surgery (CABG) was performed in patients deemed necessary according to CAG results. Kidney transplantation was performed 3 to 6 months after coronary revascularization.

Statistical Analysis

SPSS 26 program was used to evaluate the data obtained in the study. The normality of the distribution was determined by the Kolmogorov-Smirnov test. Results were expressed as mean $\pm$ standard deviation. Normally distributed variables were compared with Student's T test, and non-normally distributed variables were compared with Mann Whitney-U test. Chi-square test was used to compare categorical variables. P value less than 0.05 was considered statistically significant. Pearson analysis was used for continuous variables and Spearman test was used for non-continuous variables in the correlation analysis. The correlation coefficient (r) was calculated. Independent determinants of coronary artery disease were ascertained by univariate and multivariate logistic regression analysis.

RESULTS

The most common etiological factors for the development of ESRD were HT and DM. ESRD was defined as idiopathic in 21 patients (12.42%) whose etiopathogenesis could not be determined clearly. Less common etiologies such as horseshoe kidney, Alport syndrome, renal agenesis, vesicoureteral reflux were classified as others (**Table 1**).

Table 1. Etiologies of end stage renal disease in kidney recipients

Etiology	
Hypertension n (%)	21 (12.42)
Diabetes mellitus type 1 n (%)	4 (2.36)
Diabetes mellitus type 2 n (%)	20 (11.83)
Polycystic kidney disease n (%)	14 (8.28)
Idiopathic n (%)	21 (12.42)
Ig A nephropathy n (%)	15 (8.87)
Focal segmental glomerulosclerosis n (%)	14 (8.28)
Glomerulonephritis n (%)	9 (5.32)
Vasculitis n (%)	12 (7.1)
Amyloidosis n (%)	6 (3.55)
Nephrolithiasis n (%)	6 (3.55)
Others n (%)	27 (15.97)

The mean age of the patients was 42.86 ± 12.97 years and 43.19% were female. Ninety seven patients (57.4%) were undergoing dialysis, 4 of whom were on peritoneal dialysis. Renal transplant was performed from a cadaver in two patients and from a living donor in the other patients. The most common CV risk factors were HT and HL. Calcium channel blockers (CCBs) and beta blockers were the most preferred antihypertensive agents. (Table 2). Preoperative laboratory findings of the study group are shown in Table 3.

Table 2. Demographic and clinical characteristics of the study group	
Parameter	Study group (n=169)
Age	42.86 ± 12.97
Female, % (n)	43.19 (73)
BMI, (kg/m ²)	25.67 ± 5.57
Hypertension, % (n)	83.43 (141)
Hyperlipidemia, % (n)	35.50 (60)
Diabetes mellitus, % (n)	14.20 (24)
Smoking, % (n)	30.76 (52)
CAD, % (n)	17.15 (29)
CHF, % (n)	6.50 (11)
AF, % (n)	1.18 (2)
Antiaggregant therapy, % (n)	17.75 (30)
ACEI /ARB, % (n)	15.38 (26)
Beta blockers, % (n)	46.15 (78)
CCBs, % (n)	60.94 (103)
Statin, % (n)	15.38 (26)
Dialysis, % (n)	57.4 (97)
BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; AF, atrial fibrillation; ACEI, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCBs, calcium channel blockers.	

Table 3. Laboratory and echocardiographic characteristics of the patients	
Parameter	Study group (n=169)
Glucose mg/dl	117.97 ± 59.01
BUN mg/dl	66.75 ± 25.46
Creatinine, mg/dl	7.30 ± 2.62
eGFR (ml/min/1.73m ²)	8.49 ± 3.95
Sodium (mmol/L)	139.07 ± 4.13
Potassium (mmol/L)	4.96 ± 0.75
Total cholesterol (mg/dl)	195.90 ± 51.14
LDL (mg/dl)	128.37 ± 46.78
HDL (mg/dl)	45.93 ± 17.06
Triglycerides (mg/dl)	171.08 ± 114.19
LV EF (%)	58.22 ± 6.84
sPAP (mmHg)	28.34 ± 7.17
LVH % (n)	40.2 (68)
BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LDL, low density lipoprotein; HDL, high density lipoprotein; LV EF, Left ventricular ejection fraction. sPAP, systolic pulmonary artery pressure; LVH, left ventricular hypertrophy.	

The treadmill exercise test could be performed on 130 patients and 28 patients were evaluated as positive for ischemia. Nineteen patients underwent MPS and ischemia was detected in 5 of them. Coronary

CT angiography was performed in 21 patients and obstructive CAD was found in 4 patients. Conventional coronary angiography was performed in 61 patients. Nine of them underwent to CAG without non-invasive tests due to low EF on TTE or a previous history of CAD. It was found to be normal in 32 patients. Stent implantation with PCI was performed in 10 patients, and CABG was performed in 5 patients. Follow-up with medical treatment was recommended for 11 patients. While 2 of them had chronic total occlusion, the others had thin vessels, distal lesions or non-critical (<50%) stenosis. Twenty nine patients of all patients (17.2) had CAD. It was pre-existing in 2 of them (both had CABG), while others were diagnosed in the preoperative evaluation. In 2 patients who had previously undergone CABG, all grafts were found patent and revascularization was not required (Table 4).

Table 4. Findings of preoperative non-invasive and invasive tests	
Parameter	Study group (n=169)
Treadmill exercise test, (n)	130
Ischemia negative	82
Ischemia positive	28
Non-diagnostic	20
MPS, (n)	19
Ischemia negative, (n)	14
Ischemia positive, (n)	5
Coronary CTA, (n)	21
Non-obstructive CAD, (n)	2
Obstructive CAD, (n)	4
Coronary angiography, (n)	61
Normal coronary arteries, (n)	32
Medical treatment, (n)	12
PCI, (n)	10
CABG, (n)	5
Patients with previous CABG, (n)	2
Coronary artery disease, % (n)	17.15 (29)
MPS, myocardial perfusion scintigraphy; CTA, coronary computed tomography angiography; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass graft.	

When patients were compared according to the presence of CAD, patients with CAD were significantly older, had a higher male ratio, more CV risk factors, had higher creatinine levels, dialysis and LVH ratios and lower LV EF (Table 5). For the development of CAD, while univariate logistic regression analysis showed that age, DM, HL, dialysis history, LV EF and LVH, were the determining factors, in multivariate logistic regression analysis, age, DM, HL and dialysis history were found as independent risk factors.

In the postoperative follow-ups, no death or acute coronary syndrome was observed during the hospitalization period. Atrial fibrillation developed in two patients, acute pulmonary edema in one patient, and pneumonia in one patient. One patient died 30 days after the operation with complications related to infection.

Table 5. Comparisons of patients according to presence of coronary artery disease

Parameter	Patients with CAD (n=29)	Patient without CAD (n=140)	p value
Age	52±11	41±12.55	<0.001
Male, % (n)	87 (20)	52.1 (76)	0.002
BMI, (kg/m ²)	27.44±4.62	25.30±5.69	0.060
Hypertension, % (n)	85.1 (23)	80 (118)	0.021
Hyperlipidemia, % (n)	65.2 (15)	12.3 (18)	<0.001
Diabetes mellitus, % (n)	43.5 (10)	9.6 (14)	<0.001
Smoking, % (n)	56.5 (13)	26.7 (39)	0.004
Dialysis, % (n)	81.4 (22)	52.8 (75)	0.009
eGFR, (ml/min/1.73 m ²)	7±3.75	8.7±3.93	0.128
Creatinine, mg/dl	8.6±3.39	7.1±2.37	0.025
LV EF, %	55±8.77	59±6.35	<0.001
sPAP, mmHg	29.3±8.37	28.2±6.94	0.436
LVH, % (n)	62.1 (18)	35.7 (50)	0.008

CAD, coronary artery disease; BSA, body surface area; eGFR, estimated glomerular filtration rate; LV EF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; LVH, left ventricular hypertrophy.

Table 6. Logistic regression analyses for the presence of coronary artery disease

	Univariate analysis		
	p value	OR	95% Confidence interval
Age	<0.001	1.076	1.037-1.118
HT	0.068	0.149	0.019-1.148
DM	<0.001	0.064	0.024-0.173
HL	<0.001	0.073	0.029-0.184
Smoking	0.075	0.475	0.239-1.079
Creatinine	0.052	1.155	0.999-1.326
GFR	0.103	0.897	0.787-1.022
Dialysis	0.004	0.227	0.082-0.629
LV EF	0.015	0.941	0.896-0.988
sPAP	0.296	1.534	0.897-2.623
LVH	0.010	1.028	1.976-1.083
	Multivariate analysis		
	p value	OR	95% Confidence interval
Age	0.007	1.065	1.018-1.115
DM	0.001	0.122	0.034-0.433
HL	0.001	0.127	0.039-0.410
Dialysis	0.044	0.245	0.062-0.962
LV EF	0.260	0.953	0.877-1.036
LVH	0.448	1.572	0.489-5.049

HT, hypertension; DM; diabetes mellitus; HL, hyperlipidemia; GFR, glomerular filtration rate; LV EF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; LVH, left ventricular hypertrophy.

DISCUSSION

In our study, the leading etiological factors of ESRD were HT and DM, the most prevalent CV risk factors were HT, HL, smoking and DM, respectively. Approximately 17% of the kidney recipients had coronary artery disease. While CV risk factors were significantly higher in patients with CAD, a strong association was found with age, DM, and HL.

When investigating the demographic and epidemiological characteristics of kidney transplant patients, it should be considered that the geographical features, socio-cultural

characteristics and organ transplant policies of the countries are important determining factors. In western societies, with the increasing life expectancy, more elderly people need kidney transplantation. In a study by Luxardo et al.¹⁹ comparing the epidemiologic characteristics of patients on renal replacement therapy in Europe and Latin America, 56.2% of patients in Europe were 65 years of age or older, compared to 38.3% in Latin America. In our study, there were 7 patients (4.14%) aged 65 and over, and the mean age of the study group was relatively younger. It may be related to the fact that the research was based on a small-scale single-center data analysis and included a higher proportion of patients with congenital and genetic kidney disease. Despite of younger cohort in our study, age was significantly higher in CAD patients and was found to be an independent risk factor for the development of CAD. Additionally, consistent with the literature, there was a male predominance in the study group and the most common etiologic factors for ESRD were DM and HT.^{20,21}

The prevalence of traditional CV risk factors, particularly HT, was high in our study, similar to previous studies.^{22,23} Hypertension may occur both as a cause and a consequence of chronic renal diseases.²⁴ In our study, HT was present at a high rate of 83% of the patients, whereas hypertensive ESRD was defined in only 12% of the patients. Either way, the presence of HT has been shown to be associated with adverse CV events, increased graft failure, and death in kidney transplant recipients.²⁵ It is essential to keep blood pressure at optimal levels before and after transplantation. Although the prevalence of HT was significantly higher in the patients with CAD than in those without CAD, it was not demonstrated as an independent predictor in the logistic regression analysis.

Diabetes mellitus, HL, and smoking history were also significantly higher in the CAD group, although there were significant associations between these factors and CAD in univariate logistic regression analysis, only age, DM and HL were found to be independent predictors of CAD in multivariate logistic regression analysis. Diabetes mellitus is one of the important CV risk factors in ESRD patients and is associated with increased mortality in patients undergoing kidney transplantation.^{26,27} The prevalence of DM in patients awaiting kidney transplantation differs in studies from various countries.^{21,28,29} In our study, the prevalence of DM was about 14%, and it was found approximately half of the patients with CAD.

Chronic kidney disease causes dyslipidemia, which is an important risk factor for CV diseases, by causing impairment in lipid metabolism.³⁰ Statin use has been shown to improve lipid levels and reduce CV events in pre-end stage kidney disease and after transplantation.^{31,32}

In the present study, 35% of the patients had HL while the rate of statin use was 15%.

As for smoking, a study by Kasiske et al.³³ in which approximately 24% of the subjects were smokers, demonstrated the association of smoking with increased graft failure, death, and CV events in kidney transplant recipients. It has also been shown that smoking cessation 5 years before transplantation reduces graft failure and mortality, but does not affect the frequency of CV events. In our study, approximately 30% of the patients were smokers, and this rate was 56% in patients with CAD, which was more than twice as high that in patients without CAD, but it was not found to be an independent risk factor for the development of CAD.

Apart from traditional risk factors, it has been shown in various studies that LVH is associated with increased CV risk in patients with chronic kidney disease. It has also been demonstrated that a decrease in LV wall thickness results in better outcomes after kidney transplantation.^{34,35} In our study, consistent with the literature, LVH was significantly higher in CAD patients and was associated with the development of CAD.

There is no consensus on preoperative cardiac evaluation guidelines or expert opinions, most of them focuses on presence of symptoms and advanced age for further cardiac evaluation.^{36,37} Nevertheless, due to insufficient exercise capacity and comorbidity burden, individuals with CKD may be considered asymptomatic despite significant cardiovascular disease.³⁸ In our study, although the patients were asymptomatic for angina, most of them had normal LV systolic function and ECG findings, and were relatively young, CAD was detected in approximately one fifth of the patients. Postoperative acute coronary syndrome and cardiac death were not observed after both medical and interventional treatments applied in line with the preoperative assessment.

The main limitation of our study is that it was conducted in a small single-center cohort. Patients are heterogeneous with regard to ESRD etiology. In addition, the study included a small number of elderly patients who had a greater risk of developing cardiovascular disease. The strength of this study is that all patients were examined in terms of cardiovascular diseases, first with noninvasive and then, if necessary, invasive tests.

CONCLUSION

CV risk factors are common in kidney transplant candidates. Our findings support the need for a detailed cardiac evaluation and effective management of CV risk factors in patients preparing for kidney transplantation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Koç University Ethics Committee (Date: 26.08.2019, Decision No: 2019.265.IRB2.087).

Informed Consent: Because the study was designed retrospectively, no written informed consent d-form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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